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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Kanji TAKADA	:	Group Art Unit.: 1616
Serial No.: 09/787,612	:	Examiner: Sharmila S. Gollamudi
Filed: March 20, 2001	:	

Title: ORAL DRUG DELIVERY SYSTEM FOR ENHANCING THE BIOAVAILABILITY OF ACTIVE FORM OF GLYCYRRHIZIN

BRIEF ON APPEAL

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed on March 18, 2003, herewith are three copies of Appellants' Brief on Appeal. The attached check includes the statutory fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 10-19 of the above-identified application.

(1) REAL PARTY IN INTEREST

The real party in interest in the present application is Amato Pharmaceutical Products, Ltd., to whom the present application was assigned on February 15, 2001.

(2) RELATED APPEALS AND INTERFERENCES

There are no known related appeals or interferences.

(3) STATUS OF THE CLAIMS

Claims 10-26 are pending in the present application. Claims 20-25 were withdrawn from consideration. Claims 10-19 were rejected. Claims 10-19 are on appeal.

(4) STATUS OF AMENDMENTS AFTER FINAL

Amendments filed after final were entered.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to a drug delivery system for oral administration of glycyrrhizin. See specification page 1, paragraph [0001]. The oral delivery system contains the glycyrrhizin in a shaped core enclosed in a coating film of ethylcellulose that collapses in the colon releasing the glycyrrhizin contained therein. See page 11, paragraph [0039]. The delivery system enhances the bioavailability of active glycyrrhizin in oral route to a therapeutically effective level. See page 2, paragraph [0005].

(6) ISSUES

The issues outstanding in this application are the rejections under 35 U.S.C. § 103:

(1) whether claims 10, 11, 12 and 19 are unpatentable over Takakazu (JP 3-255037) in view of Takada (US 5,637,319),

(2) whether claims 13 and 15 are unpatentable over Takakazu (JP 3-255037) in view of Takada (US 5,637,319), in further view of Sipos (US 4,079,125),

(3) whether claims 14 and 16 are unpatentable over Takakazu (JP 3-255037) in view of Takada (US 5,637,319), in further view of Masanobu (JP 10226650), and

(4) whether claims 17 and 18 are unpatentable over Takakazu (JP 3-255037) in view of Takada (US 5,637,319), in further view of Antoku (US 5,434,142).

(7) GROUPING OF THE CLAIMS

For the purpose of this appeal,

claims 10, 11, 12 and 19 are considered to stand or fall together for issue number 1,

claims 13 and 15 are considered to stand or fall together for issue number 2,

claims 14 and 16 are considered to stand or fall together for issue number 3, and

claims 17 and 18 are considered to stand or fall together for issue number 4.

(8) APPELLANTS' ARGUMENTS

Issue (1) - whether claims 10, 11, 12 and 19 are unpatentable over Takakazu (JP 3-255037) in view of Takada (US 5,637,319)

JP 3-255037 teaches a glycyrrhizin preparation coated with an enteric film. See abstract.

However, JP 3-255037 fails to teach or suggest the device for colon-targeted oral delivery of claim 19, and its dependent claims or of claim 10. Nowhere does this reference, for example, teach or suggest a shaped core made of a glyceride suppository base that melts or liquefies at the body temperature.

Instead, the reference teaches a liquid dispersion in a coated capsule (Example 1), coated granules (Example 2), and a liquid dispersion in soft capsules (Example 3).

Examples 1 and 3 of the reference are directed to dispersions dissolved in "Invider 742," identified as a mixture of mono-, di- and tri-glycerides of capric (C_{10}) acid and caprylic (C_8) acid. Both of these dispersions are believed to be liquid at room temperature. Example 3 specifically states that the dispersion is liquid, and Example 1, states that the dispersion was filled into a capsule.

The fact that these dispersions were liquid at room temperature is also supported by the absorption test discussed on page 7 of the reference, wherein a dispersion of glycyrrhizin monoammonium salt in Invider 472 was administered to the duodenum of rats. Upon belief, a dispersion other than liquid can not be directly administered to the duodenum of rats.

Example 2 of the reference is directed to granules formed from pulverized glycyrrhizin and stearic (C_{16}) acid monoglyceride. The number of carbon atoms are larger for stearic (C_{16}) acid monoglyceride than for capric (C_{10}) acid and caprylic (C_8) acid. Thus, the components are solid in form and the resultant dispersion is in the form of granules, and not a liquid. However, granules, while not a liquid, nevertheless do not teach or suggest a shaped core.

Additionally, JP 3-255037 teaches an enteric coating that is dissolved in the duodenum. See abstract and page 3, lines 8-9. Thus, the coating of the primary reference does not rupture selectively in the colon by the internal pressure generated by the peristalsis of the intestine as in the claimed invention.

The Examiner in the Final Rejection appeared to construe the term "enteric" in the reference based on a dictionary differently, i.e. more broadly than defined by the reference,

even though a clear definition is provided by the reference. The dictionary definition from Webster's dictionary, i.e., "medical preparation treated to pass through the stomach unaltered and disintegrated in the intestines," is improperly read into the definition of the term in the reference because JP 3-255037 specifically and clearly teaches that the enteric film is dissolved in the duodenum. Nowhere does JP 3-255037 teach or suggest that the film enclosing the liquefied core ruptures selectively in the colon by the internal pressure generated by the peristalsis of the intestine. Broadening the teaching of the reference based on a dictionary definition of a term therein is improper when the reference itself clearly defines the scope of such a term. One of ordinary skill in the art would have construed the definition of enteric in accord with the teachings of the reference and not in accord with a broader dictionary definition. The context of the patent makes it clear that the term "enteric" therein defines a coating that dissolves. The meaning of the term "enteric" in the reference is clear and not varied. Thus, one of ordinary skill in the art would understand and read said term in the context of the invention of the reference to refer to a coating that dissolves and would not be motivated to go to a dictionary to further define said term, as its meaning is clear and complete in the specification.

JP 3-255037clearly sets out key features of the invention therein including a coating that dissolves. No evidence is present which would indicate that the reference's authors envisioned an enteric coating that ruptures. There is no evidence of a suggestion or teaching which would provide the requisite motivation to one of ordinary skill in the art to use a coating that ruptures instead of dissolves. Cases in the context of claim construction, which is a different situation, but may be relevant here, state that the "best source for understanding a technical term is the specification from which it arose. ... When the specification explains and defines a term ... without ambiguity or incompleteness, there is no need to search further for the meaning of the term." *Multiform Desiccants v. Medzam*, 45 USPQ2d 1429 (CAFC 1998), (holding the meaning of "degradable" in claims limited to the dissolution of an envelope as described in the specification, and excludes a meaning wherein the envelope "degrades" by bursting instead of dissolving). Likewise in the present situation, the meaning of "enteric" of the reference should be interpreted as defined in the specification, i.e., to refer to a coating that dissolves, and not more broadly to include a definition which includes bursting.

Thus, nowhere does JP 3-255037 teach or suggest a shaped core made of a glyceride suppository base that melts or liquefies at the body temperature, or a coating that ruptures

selectively in the colon by the internal pressure generated by the peristalsis of the intestine as in the claimed invention.

US 5,637,319 also does not offer any teaching or suggestion for the preparation of a shaped core.

US 5,637,319 teaches an ethylcellulose capsule which is disintegrated by the inner pressure of the large intestine. See column 3, lines 1-14. One of skill in the art would not have been motivated to select this capsule for the dispersions or granules of JP 3-255037 since the latter are directed to increasing the concentration of glycyrrhizin in the blood when released in the duodenum, which is the beginning portion of the small intestine, starting at the lower end of the stomach and extending to the jejunum. Thus, the coating taught by US 5,637,319 would not have achieved the objectives of JP 3-255037, i.e., to deliver the dispersions to the duodenum.

Furthermore, none of the cited references teach or suggest an ethylcellulose film coating that is continuous around a shaped core as in claim 19. JP 3-255037 teaches enteric films which dissolve in the duodenum. Some specific compounds for the formation of the films are named on page 3, lines 13-16. Ethylcellulose is not among them. US 5,637,319 teaches a variety of capsules, one of which is an ethylcellulose capsule. However, that capsule is formed by coating the inner or outer surface of a conventional gelatin capsule body and then dissolving the gelatin in warm water. See column 7, lines 59-64, and column 8, lines 15 to 18. Further, US 5,637,319 teaches that a pore is made in the capsule to fill the drug into the capsule followed by closing the pore with ethylcellulose glue or by capping the opening with an ethylcellulose cap. See column 8, lines 18-35, and Examples 4 to 6. Therefore, the final product of US 5,637,319 has a capsule that either has a cap or a pore that is sealed by glue instead of a capsule of the present invention that is continuous. Thus, the coating of claim 19 differs from coatings described in each of the prior art references. No teaching or suggestion to alter the prior art coatings to be continuous is present in any of the references. Thus, the advantages, i.e., a simple inexpensive procedure to prepare the capsules of claim 19, said capsules being structurally different than the capsules of the prior art, achieved by the preparation of a coating in accord with the withdrawn process claims, is not taught or suggested by either of the references.

Also, forming a coating in accord with the present invention would not be possible in view of the liquid dispersions of the primary reference. One would not be able to dip the liquid dispersion in a solution of ethylcellulose to form a film that is continuous around said

liquid dispersion, as can be done with a shaped core. As for the granules, the reference only teaches and suggests their coating with a coating that dissolves in the duodenum, i.e., one of the mentioned coatings on page 3 that is taught to dissolve in the duodenum.

The Office Action alleges that "the intended use of the enteric coating whether is dissolved or ruptured, does not hold patentable weight unless a structural difference in the end product is shown." The test for obviousness is whether the combined teachings of the references would have suggested the claimed invention to those of ordinary skill in the art. The current invention is directed to a device for colon-targeted oral delivery that has several features that are not taught or suggested in the prior art references. These features make the claimed oral delivery device structurally different than the prior art devices in at least having a shaped core that melts or liquefies at body temperature, an ethylcellulose coating over said shaped core, and/or a continuous (see claim 19) coating film of ethylcellulose enclosing said shaped core.

Additionally, even if one were to view the broad dictionary definition as controlling in the JP 3-255037 reference, which is not the case, a reference must be evaluated not for only what it teaches broadly, but also for what it fairly suggests to a skilled artisan, i.e., what it specifically motivates the artisan to do to practice the taught art. While a broad teaching or goal of an invention may motivate an artisan to try a variety of solutions to a recognized problem, i.e., make it obvious to try, it does not render all solutions to said problem obvious. The standard in patent law is not obvious to try. "A general incentive or recognition of a problem does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995). Thus, a general incentive to provide an enteric coating on a given composition does not provide the motivation to use any known enteric coating. Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871 (CCPA 1981).

Thereafter, even if JP 3-255037 is construed to teach an enteric coating broadly, i.e., in accord with the alleged dictionary definition, that teaching is insufficient to render obvious any specific enteric coating without further evaluating what the reference specifically suggests. JP 3-255037, as discussed above, teaches the delivery of glycyrrhizin to the duodenum, while the secondary reference teaches a capsule that ruptures in the large intestine. No motivation is thus present to use the capsule of the secondary reference for the delivery of the drugs of the primary reference. The claims are thus not obvious.

Reversal of the rejection is therefore mandated by law, and is respectfully and courteously requested.

With respect to the remaining rejections, all are over dependent claims only and are over the two references discussed in this rejection in combination with additional references. It is urged that if the independent claims in this rejection are found allowable, all dependent claims would be readily allowable as well. Nevertheless, each of the rejections is separately discussed.

The arguments from this section relating to the primary and secondary references in each of the rejections are incorporated therein in their entirety, and thus, will not be repeated each time.

Issue (2) - whether claims 13 and 15 are unpatentable over Takakazu (JP 3-255037) in view of Takada (US 5,637,319), in further view of Sipos (US 4,079,125)

US 4,079,125, the tertiary reference, in further view of the primary and secondary references discussed above, allegedly teaches enteric coatings and dusting talc to prevent aggregation of tablets.

US 4,079,125 only teaches "an enteric coating polymer having the necessary properties to survive gastric conditions for at least about 1 hour, preferably 2 hours, and readily disintegrate in the duodenum under neutral to alkaline pH." See column 8, lines 33-37. Nowhere does this reference teach or suggest an enteric coating that ruptures selectively in the colon by the internal pressure generated by the peristalsis of the intestine.

With respect to the use of dusting talc, the reference teaches their use to prevent the rapid aggregation of the tablets or the beads into multiples. See column 8, lines 65-69. The present invention concerns the use of talc over a shaped core. No specific teaching to this effect is found in the reference.

Issue (3) - whether claims 14 and 16 are unpatentable over Takakazu (JP 3-255037) in view of Takada (US 5,637,319), in further view of Masanobu (JP 10226650)

JP 10226650, the tertiary reference, in further view of the primary and secondary references discussed above, allegedly teaches a preparation containing glycyrrhizin and an enteric coating that dissolves in the large intestine.

JP 10226650 teaches a formulation of glycyrrhizin and an absorption promoter. The absorption promoter is an agent that solubilizes the formulation. JP 10226650 teaches that because

> an intestinum crassum [identified as part of the alimentary canal lower part] is a site which absorbs moisture, moisture is not fully supplied like the alimentary canal upper part, but it has very little moisture within the normal intestinum crassum. Therefore, the improvement of sufficient absorption did not accept only by sending a solid medicine and a solid absorption accelerator simply to an intestinum crassum. Then, the solubilizing agent of this invention solves this trouble by solubilizing a solid medicine and a solid absorption accelerator.

See paragraphs [0008] and [0009]. The examples in the reference also only teach the preparation of a solution. See paragraphs [0027]-[0037]. Nowhere does this reference teach or suggest the use of a shaped core being made of a suppository base comprising glyceride that melts or liquefies at the body temperature.

While JP 10226650 appears to have recognized a problem that it is desirable to supply moisture with a solid medicament to the intestinum crassum, the only solution taught or suggested was to solubilize the medicament prior to encapsulation. While the recognition of a problem may motivate an artisan to try a variety of solutions to a recognized problem, i.e., make it obvious to try, it does not render all solutions to said problem obvious. The standard in patent law is not obvious to try. "A general incentive or recognition of a problem does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995). Thus, a general recognition that a medicament directed to the intestinum crassum does not provide the motivation to render obvious all solution to said problem, such as, for example, the use of a shaped core being made of a suppository base comprising glyceride that melts or liquefies at the body temperature. Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d

413, 425, 208 USPQ 871 (CCPA 1981). None of the references teach or suggest the shaped core of the present invention. Thus, the claims are not obvious.

With respect to the enteric coating taught in JP 10226650, the reference teaches a large variety of enteric coatings. See paragraphs [0019] and [0020]. No specific teaching is presented with respect to the claimed enteric coating, or the mechanism by which the glycyrrhizin is to be released.

Issue (4) - whether claims 17 and 18 are unpatentable over Takakazu (JP 3-255037) in view of Takada (US 5,637,319), in further view of Antoku (US 5,434,142)

US 5,434,142, the tertiary reference, in further view of the primary and secondary references discussed above, allegedly teaches dosages for glycyrrhizin for the treatment of muscular dystrophy.

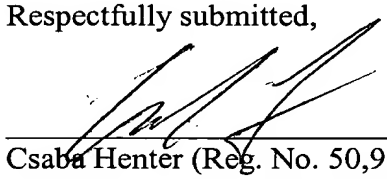
This reference does not cure the deficiencies of the primary and secondary references. It provides no motivation to a shaped core as claimed or to a coating as claimed. It teaches that the pharmaceutical agent containing glycyrrhizin "may be used in the form of injections and internal medicines such as powders, tablets, granules, capsules, solutions and the like." See column 2, lines 20-25.

The fact that ranges are recited for glycyrrhizin in conjunction with a broad teaching of the above-recited forms would not motivate an artisan to select a dose regiment for the specific claimed invention herein, where the glycyrrhizin is delivered to the colon where uptake of the glycyrrhizin is influenced by a variety of factors not considered by the reference. See, for example, discussion relating to glycyrrhizin uptake in the intestinum crassum discussed above in the rejection over JP 10226650 as the tertiary reference.

Conclusion

Applicants submit that none of the claims are taught or suggested by the references. Thus, the claimed invention is not obvious over the references. Reversal of the rejection is therefore mandated by law, and is respectfully and courteously requested.

Respectfully submitted,



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APPENDIX

10. A device for colon-targeted oral delivery of glycyrrhizin comprising a shaped core containing an amount of glycyrrhizin, said shaped core being made of a suppository base comprising glyceride that melts or liquefies at the body temperature, and a coating film of ethylcellulose enclosing said shaped core and having a film thickness whereby when the device is transported through the digestive tract to the colon, the film enclosing the liquefied core ruptures selectively in the colon by the internal pressure generated by the peristalsis of the intestine.

11. The device according to claim 19, wherein said amount of glycyrrhizin is in excess of the amount needed for compensating for the hydrolysis thereof by the intestinal flora.

12. The device according to claim 19, wherein said coating film is formed by dipping the shaped core in a solution of ethylcellulose.

13. The device according to claim 12, wherein said shaped core is dusted with a powder to prevent from sticking before dipping.

14. The device according to claim 19, wherein said shaped core further contains an absorption promoter for glycyrrhizin.

15. The device according to claim 13, wherein the powder is talc.

16. The device according to claim 14, wherein absorption promoter is an organic acid, a surfactant, a chelating agent, or a mixture thereof.

17. The device according to claim 19, wherein the device contains 10 to 1,000 mg of glycyrrhizin.

18. The device according to claim 19, wherein the device contains 100 to 800 mg of glycyrrhizin.

19. A device for colon-targeted oral delivery of glycyrrhizin comprising a shaped core containing an amount of glycyrrhizin, said shaped core being made of a glyceride suppository base that melts or liquefies at the body temperature, and a continuous coating film of ethylcellulose enclosing said shaped core and having a film thickness whereby when the device is transported through the digestive tract to the colon, the film enclosing the liquefied core ruptures selectively in the colon by the internal pressure generated by the peristalsis of the intestine.

20. A process for preparing a colon-targeted oral delivery device of glycyrrhizin comprising:

(a) adding glycyrrhizin to a glyceride suppository base that melts or liquefies at the body temperature while the suppository base is in molten or liquefied state to obtain a suspension;

(b) casting the suspension in a mold;

(c) cooling the mold to obtain a shaped solidified core of the suspension;

(d) enclosing the resultant shaped core with a continuous coating film of ethylcellulose, the coating film having a film thickness whereby when the device is transported through the digestive tract to the colon, the film enclosing the liquefied core ruptures selectively in the colon by the internal pressure generated by the peristalsis of the intestine.

21. The process according to claim 20, wherein the amount of glycyrrhizin in said suspension is in excess of the amount needed for compensating for the hydrolysis of glycyrrhizin by the intestinal flora.

22. The process according to claim 20, wherein said coating film is formed by dipping the shaped core in a solution of ethylcellulose.

23. The process according to claim 20, wherein said suspension further contains an absorption promoter for glycyrrhizin.

24. The process according to claim 20 further comprising dusting the shaped core with powder before (d) to prevent sticking of the shaped core together.

25. The process according to claim 24, wherein the powder is talc.

26. The colon-targeted oral delivery device prepared by the process of claim 20.